UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,476	10/09/2001	Ralph C. Budd	1974.003	5318

7590 10/21/2003

Kathy Smith Dias, Esq.
HESLIN ROTHENBERG FARLEY & MESITI P.C.
5 Columbia Circle
Albany, NY 12203

EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,476	BUDD ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *4,7 and 9-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

DETAILED ACTION

Claims 1-21 are pending.

1. Applicant's election with traverse of Group II, claims 1-3, 5-6 and 8 in Response to Restriction Requirement , filed on 08/14/03 is acknowledged. Applicant traverse the Restriction Requirement on the grounds that the search of Groups I-II together would not constitute a serious search burden on the examiner and that search of the claims of Group I would provide useful information for the claims of Group II.

This is not found persuasive because the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criteria and therefore establishes that serious burden is placed on the examiner by the examination of more than one Group. The Inventions are distinct for reasons elaborated in paragraphs 3-5 of the previous Office Action and above.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4, 7 and 9-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-3, 5-6 and 8 drawn to a method of suppressing the immune system comprising administering a modified caspase-8 inhibitor are under consideration in the instant application.

2. This application contains sequences disclosures (IETD, YVAD, ZVAD on page 5, paragraph 0018 and page 6, paragraph 0022 and claims) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Applicant is reminded to amend the specification and the claims accordingly.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 04/06/1999. It is noted, however, that applicant has not filed a certified copy of the 19915465 application as required by 35 U.S.C. 119(b).

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 5-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses detailed *in vitro* assays of the ability of 3 caspase inhibitors YVAD-fmk, zVAD-fmk and IETD-fmk to inhibit proliferation of T cells stimulated with anti-CD3 antibodies (Example 1 and 2 of the Specification as filed). The specification does not adequately teach how to effectively suppress the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor. Moreover, no animals models were used to study the effectively of suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an

effective amount of any caspase-8 inhibitor. Since there is no animal model studies and data in the specification to show the effectively of suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor, it is unpredictable how to correlate *in vitro* results with *in vivo* use. Feldman et al (Transplantation proceedings, 1998, Vol.30, pages 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al . further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Moreover, since the method of suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor can be species- and model-dependent (seeVan Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. Moreover, an effective protocol for suppressing the immune system of a human after allogenic cell, tissue or organ transplantation is subject to a number of factors which enter the picture beyond simply the administration to the subject an effective amount of any caspase-8 inhibitor Demonstrating *in vitro* assays of the ability of 3 caspase inhibitors YVAD-fmk, zVAD-fmk and IETD-fmk to inhibit proliferation of T cells stimulated with anti-CD3 antibodies (Example 1 and 2 of the Specification as filed) cannot alone support the predictability of suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering to the subject an effective amount of any caspase-8 inhibitor . Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Bals R., et al., (Infection and Immunity, 1999, v.67, pages 6084-6089) teach that functional studies have been restricted primarily to *in vitro* experiments with purified peptides and do not necessarily reflect the complexity of *in vivo* interaction, such as synergism and antagonism between individual substances (see overlapping pages 6087-6088 in particular). Also, an effective protocol for suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor the absence of *in vivo* data are unpredictable for the following reasons: (1) the caspase-8 inhibitor may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the caspase-8 inhibitor may not reach the target area because, i.e. the caspase-8 inhibitor may not be able to cross the mucosa or the caspase-8 inhibitor may be adsorbed by fluids, cells and tissues where the caspase-8 inhibitor has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See

page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Therefore, it is not clear that the skilled artisan could predict the efficacy of a method suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the subject or patient. In the absence of additional information the skilled artisan would not have been able to use the undisclosed compound for treatment without undue experimentation.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of suppressing the immune system of a human after allogenic cell, tissue or organ transplantation by administering an effective amount of any caspase-8 inhibitor in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

5. No claim is allowed.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
October 20, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600